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Short communication

A perspective on the economic valorization of gene manipulated biotechnology: Past and future☆

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ABSTRACT

Three distinct fields of gene manipulated biotechnology have so far been economically exploited: medical biotechnology, plant biotechnology and industrial biotechnology. This article analyzes the economic evolution and its drivers in the three fields over the past decades, highlighting strong divergences. Product and market characteristics, affecting firms' financing options, are shown to be important enablers or inhibitors. Subsequently, the lack of commercialization in a fourth type of gene manipulated biotechnology, namely environmental biotechnology, is explained by the existence of strong barriers. Given the latter's great promises for environmental sustainability, we argue for a need to push the commercial valorization of environmental biotechnology. Our research has strong implications for (technology) management research in biotechnology, pointing to a need to control for and/or distinguish between different biotechnology fields.

1. Introduction

Biotechnology has been defined in many different ways. An early definition reads: "biotechnology is the application of biological organisms, systems, or processes to manufacturing and service industries" [1]. Most definitions encompass fermentation processes from wine to penicillin, as well as a broad spectrum of contemporary technologies that have grown out of recombinant DNA technology [1]. A number of biotechnological fields that have traditionally been distinguished include health, agriculture, food and beverages processing, natural resources, environment, industrial processing and bioinformatics [2]. This paper specifically focuses on the valorization of gene manipulated biotechnology (or genetic engineering). Gene manipulated biotechnology is the deliberate modification of the characteristics of an organism by the manipulation of its genetic material and is a subdomain of biotechnology [3]. This paper aims at providing an understanding of how gene manipulation technologies have been economically exploited and what factors have driven this evolution. So far, economical valorization of gene manipulated biotechnology has mainly occurred in three fields: (i) medical biotechnology (referring to applications in the health care sector); (ii) plant biotechnology (referring to applications in agriculture) and (iii) industrial biotechnology (referring to applications in industrial processes such as manufacturing and chemical processes). While the originating technology for the three fields is similar [4], their economic valorization differs strongly. In what follows we provide an understanding of the evolution of valorization in the medical, plant and industrial gene manipulated biotechnology industries and its driving forces. We subsequently show that these forces have led to a fourth field of gene manipulated biotechnology, namely environmental biotechnology, to be hardly commercially exploited. We argue that this exploitation is however highly desirable from a social and environmental perspective. We subsequently elaborate on the desirability for future research to account for the differences in the biotechnology fields.

2. Industry evolution

The medical biotechnology industry originated in the United States. Laws facilitating technology transfer as the Bayh–Dole Act (1980) gave incentives to universities to commercialize research

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and allowed academics to establish companies while retaining their positions at the university. This helped stimulating the establishment of many new biotechnology firms and the overall biotech industry [4]. Specifically for California, where the biotech industry originated, other stimulating ingredients were the presence of scientists with commercial ideas, mobile labor, knowledgeable finance in the form of venture capital investors and strong communication networks [4,5]. The latter were inherited from the successful semiconductor industry in the Silicon Valley area. As most of the publicly funded research in the United States was in health care (especially in cancer-related areas), a critical mass of technological innovation was developed on which a new industry, the medical biotechnology industry, was created. Numerous science-based start-up firms were created as of the mid to late 70s [4,6], based upon scientific breakthroughs at research institutes and mainly financed with venture capital. These newly established companies were the first to successfully produce the first generation of genetically engineered human therapeutics that often allowed to treat diseases for which no therapies existed until then. Thereafter, companies specialized in new diagnostics and in animal therapeutics emerged. Several pioneering start-ups have grown organically to become fully integrated companies such as Genentech [7,8]. Today still, there are many new start-ups worldwide, often founded in collaboration with incumbent pharmaceutical companies, providing technological or financial support.

Mirroring the development in the medical biotech industry, the plant biotechnology industry originated in the 1980s through the creation of many technology-based start-up companies focused on generating solutions to make plants resistant against diseases and drought. Similarly to the development in the medical biotech industry, many of these start-up companies originated from research at universities and research institutes. Pioneering companies emerged simultaneously in the U.S. and in Europe (e.g. Plant Genetic Systems). In contrast with the medical biotechnology industry, genetically modified (GM) crops improved existing crops, rather than offering radically new products addressing unserved customer needs. GM crops thereby cannibalized the sales of traditional agrichemical companies. This induced a number of agrichemical companies to acquire smaller start-ups, in an effort to maintain profitability while investing in their future [9]. As such, the plant biotechnology industry largely followed an acquisitive growth trajectory resulting in a high degree of consolidation [7]. While there were still eleven large agrichemical companies engaging in biotechnology in 1995, next to a large amount of smaller firms, their number was reduced to only six by 2003 [9].

Industrial biotechnology has not received the level of attention heaped upon therapeutics and agricultural biotechnology. The promise of industrial biotechnology has been to reduce or replace the use of fossil energy and hydrocarbon-based materials with renewable, plant-based resources and naturally occurring micro-organisms to produce more cost-effective and environmentally friendly material for textiles, fuels, chemicals, pollution prevention and even human pharmaceuticals [9]. Producing chemicals through bio-chemical routes is still considerably more expensive compared to the traditional production routes for most products and biomass is not yet competitive with fossil fuels [9]. Hence, the economic valorization of industrial biotechnological processes has been more limited. In a first phase, it has been driven by large chemical corporations; it is only over the last five years that new start-ups emerged in this field [2].

In summary, the industrial evolution of the three gene manipulated biotechnology fields was very different. Medical biotechnology has been the first to emerge and is still the strongest [4,10]. The industry has developed through a combination of organic and acquisitive growth, with many early start-ups having grown to become fully integrated companies. Following the dominant position of medical biotechnology in the biotechnology industry, (technology) management researchers have largely focused on this industry field. The plant biotechnology field has been characterized by acquisitive growth: whereas many start-ups initially successfully applied the science of biotechnology, many got acquired by large incumbents and few start-ups survived as independent companies [9]. Finally, the industrial biotechnology field has more recently emerged in incumbent chemical companies, with new start-ups only recently entering this market.

3. Drivers of the evolution

In what follows, we elaborate on the factors that explain the differences in evolution between the biotechnology fields. First, we elaborate on the research and development (R&D) process and costs. Second, we indicate how the nature of the product and its appropriability together with the nature of the market, has driven the evolution. These factors lead to differences in the availability of financing sources which has, in turn, affected the biotechnology industry evolution.

3.1. R&D process and costs

A first important difference between the three fields relates to the R&D process and cost. The time from scientific discovery to first sales of a new drug in the medical biotechnology field is at least ten years [11]. Due to an intense regulatory framework, the average cost for a new drug to achieve regulatory approval is estimated to vary from $500 million [12] up to $800 million [13,14]. While the time for developing a new GM crop and gaining approval is comparable, the cost for developing agro-bio products is significantly lower and is estimated to be about $100 million [9]. The industrial biotechnology industry is able to bring innovations to the market in only three to five years. It has less regulatory requirements to be taken into consideration and hence can generate revenues much faster than medical or plant biotechnology [2]. While the bulk of the invested capital in medical and plant biotechnology innovations goes to intangible resources such as people, industrial biotechnology often requires expensive infrastructure such as testing sites, as innovations are often related to industrial process improvements.

3.2. Product/process and appropriability regime

A second way in which the three fields differ is the extent to which inventions can be protected through patents, leading to intellectual property (IP) rights. Intellectual property rights can lead to a strong monopoly position for the owner and higher profit margins in case of a successful product [15]. The drug development process (medical biotechnology) is characterized by high risk and low success rates in final regulatory approval, but medical biotechnology inventions, especially therapeutics, typically have a strong patent position. Similarly, the plant biotechnology is characterized by a strong appropriability regime through strong patent positions. This allows the IP owners to generate high margins that cannot be eroded by comparable products throughout the lifetime of the patent. Industrial biotechnology, in contrast, frequently focuses on innovative technologies in production processes without a distinct patentable end-product. This creates a high risk for opportunistic behavior by competitors, which may acquire and use the new technology through copying. It also makes licensing the technology to a third party risky, as the payment of royalties and fees may cease when the licensee acquired the technical knowledge. In sum, the medical and plant biotech industries were able to build upon patent-protected product innovations whereas the industrial biotech industry has mainly generated process innovations characterized by lower appropriability regimes.

3.3. Nature of the market

A third difference driving the evolution of the biotechnology fields relates to the nature of the market and includes the type of market addressed (pull versus push market), added-value from a customer perspective, public opinion and potential profit margins. The medical biotechnology industry has generated many role models where blockbuster drugs yielded extremely high returns on investment. The success of these blockbusters is to a large extent driven by the clear added-value of the new drug from a patient's perspective. In case of a common disease, this positively combines with a large market potential. Given the lifesaving possibilities of medical biotechnology, public opinion has been mainly positive toward this field. As such, the medical biotechnology has in general been characterized by a strong market pull.

By contrast, plant biotechnology addresses the agricultural industry, which is a low margin industry with a low global market growth around 2% annually. Further, GMOs improve traditional crops, but do not provide radically new products. An additional factor inhibiting economic valorization of GMOs has been the growing apprehension of consumers in certain parts of the world, including Europe, leading to legal bans on these products. Subsequently, plant biotech companies mainly have to push their products on the market by replacing traditional products in sometimes adverse conditions, which is more difficult compared to the commercialization of medical biotechnology.

Finally, the industrial biotech industry still lacks strong role models of companies and entrepreneurs which have successfully commercialized technological developments in industrial biotechnology [2]. In a first phase, this industry mainly developed new industrial processes to manufacture already available products. Technological know-how is often used in the early stage of the production process and hardly visible in the end product. More recently, industrial biotechnology also led to the development of new products, such as bioplastics or biofuels. However, the added-value of industrial biotech products compared to established products is less clear to the customer, strongly requiring a market push mechanism. Compared to plant biotechnology, industrial biotechnology has however faced less negative public opinion.

3.4. Financing sources

Whereas each of the above mentioned differences has influenced the evolution of the different biotechnology fields by itself, they have also affected an important driver of their evolution, namely the availability of financing sources for both new start-ups and established companies. The importance of the national and regional innovation systems in which biotechnology is embedded, is further not to be underestimated [16]. Within such innovation systems, public sources of financing are provided in order to fund technological developments in biotechnology [17], which are, however, often insufficient to fund the long trajectory toward successful commercialization of biotechnology inventions. Specifically, whereas investing in the early development stages requires significant amounts of financing in each biotechnology field, actors in medical and plant biotechnology need the funding for the development of IP, while actors in industrial biotechnology mainly need the funding to build infrastructure. The development in the medical and plant biotechnology fields typically follows a staged process with clear go-or-no-go decision points. This allows sequential investing, decreasing the financial risk as additional money is only invested if a previous phase was successful. In case of industrial biotechnology, however, the efficacy of a technology can often only be tested in a final, industrial scale. Subsequently, in case the technology does not perform as expected, the infrastructure does not have any residual value and the total investment is irrecoverable. As the total investment in infrastructure has to be made upfront, sequential investment is not possible making that investors risk losing a larger investment amount. The low appropriability regimes that characterize industrial biotechnology have further negatively affected the interest by financing parties.

Further, as argued previously, the nature of the market for medical biotechnology is economically more attractive compared to that for plant biotechnology, which is, in turn, more attractive than that for industrial biotechnology. This makes medical biotechnology more attractive for private external investors such as venture capital investors. Finally, external investors are concerned by the way they can sell their equity stakes in the medium term. The most successful exit routes for venture capital investors are initial public offerings (IPOs) and trade sales, in which the entrepreneurial companies are acquired by industrial

Table 1
Drivers of the evolution in medical, plant and industrial biotechnology.

Driver	Medical	Plant	Industrial
Industry origination	Research at universities and research institutes	Research at universities and research institutes	Research at large chemical corporations
R&D timeline	Long time	Long time	Shorter time
Development cost	High, sequential investment	Medium, sequential investment	Medium, up-front investment (infrastructure)
Product/process	Product	Product	Initially process followed by product
Appropriability of IP	Strong	Strong	Weak
Nature of the market	PULL Market potential: high High margins Public opinion: PRO	PUSH Market potential: high Lower margins Public opinion: AGAINST	PUSH Market potential: unclear Lower margins Public opinion: NEUTRAL to PRO
Investor exit opportunities	Many (IPOs and acquisitions)	Few (mainly acquisitions, some IPOs)	Unexplored
Venture capital interest	High	Medium (decreased)	Low but growing

players [18]. Incumbent pharmaceutical companies often acquire medical biotechnology start-ups that have successfully passed critical stages in the FDA approval process. Given the large number of acquisitions and IPOs of medical biotech start-ups, there has always been a wide range of exit opportunities for successful companies active in medical biotechnology. The strong IP positions, the pull nature of the market thanks to clear added-value to the customer, and the possibility of sequential investing coupled with valuable exit options, offset the high levels of technological risk and make medical biotechnology an interesting field for private investors. This explains why the medical biotechnology field has been characterized by a large number of start-up companies financed by venture capital [19,20].

In plant biotechnology, exit opportunities used to include acquisitions by industrial players, but these have lately dwindled down due to a strong consolidation in the industry. Fewer exit options for private investors, together with less attractive commercial margins and the pull nature of the market in combination with an increasingly negative public opinion in certain parts of the world, made this industry less attractive to private early stage investors. This, in turn, led to a decrease in the number of plant biotech start-ups. Currently, technological developments mainly take place within large agrichemical companies. Finally, in industrial biotechnology, the difficulties to get a new genetic development appropriated, the fierce competition, the large upfront and irrecoverable investment in infrastructure and the relatively weak pull of the market for innovative products, have resulted in venture capital investors turning toward other investment areas. Consequently, a relatively low number of start-up companies have been created in industrial biotechnology and developments in industrial biotechnology have so far mainly taken place in large chemical companies. Table 1 summarizes the main drivers.

4. Future evolution

This paper has highlighted the different routes to economic valorization and industrial evolution in three biotechnology fields involving gene manipulation. The main drivers for the industry evolutions are related to R&D, product and market characteristics which have subsequently affected the availability of external financing for biotech developments. By consequence, the availability of financing for entrepreneurial companies has strongly driven the degree to which entrepreneurial companies have been established in a specific field, or alternatively how important incumbents have driven economic valorization. Our analysis of the different industry fields and their evolution gives rise to theoretical and practical implications.

First, our observations lead to a number of recommendations for management researchers. Specifically, so far, researchers studying the biotechnology industry have either focused on the broader biotech industry or have focused on specific industry fields or technologies, very often medical biotechnology. Nevertheless, the latter researchers have often drawn conclusions for the entire industry, without acknowledging the vast differences between biotechnology fields [20]. As such, we call for future research to either control for the industry field in biotechnology or to dedicate attention to the extent to which conclusions can be generalized beyond the medical biotechnology industry.

Second, our analysis has a number of practical implications. Remarkably, there are currently few companies which apply a fourth type of gene-manipulated biotechnology, namely environmental biotechnology. This field focuses on improvements in downstream processes, striving for a healthier and more hygienic environment thereby increasing the overall quality of life and fostering long-term sustainability. While the field of environmental biotechnology originated in the 1970s, it has incorporated gene manipulation since the 1990s. This has produced interesting technological breakthroughs, but commercialization thereof is limited. This field differs from the ones analyzed above as it has so far mainly focused on removing unwanted chemicals (pollutants) and materials (waste), and as such has not directly generated economic returns. The lack of commercialization so far can also be explained using the drivers identified before. While the development trajectory and cost of environmental biotechnology is comparable to that of plant and industrial biotechnology, it mainly generates process technologies which are hard to protect. Further, while waste reduction is socially desirable, this is typically not (correctly) priced in the market. Hence, firms are not able to internalize the social value they could create by adopting these technologies. This is a typical case of positive externalities at the societal level which cannot be appropriated by individual firms. In addition, public opinion is negative vis-à-vis these GM technologies in certain parts of the world. Given these adverse economic conditions, neither incumbent firms nor start-ups are inclined to exploit environmental biotechnology innovations. This may change in the future as environmental biotechnology is strongly becoming re-oriented toward up-cycling of 'used materials' in the framework of providing a cyclic economy which helps to abate the putative dramatic negative consequences of climate change.

We conclude that differences in economic valorization of GM biotechnology can be explained by market mechanisms. Market mechanisms lead to market failures in the case of environmental biotechnology, however: technological developments are exploited to a lesser extent than would be optimal from a larger societal perspective, and more specifically an environmental sustainability perspective. We argue therefore that public policy intervention is needed in order to embrace gene-manipulated environmental biotechnology and exploit environmental biotechnological technological progress to its full potential.

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